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Drinking Water Health Advisory for Perfluorooctanoic Acid (PFOA)

**Drinking Water Health Advisory
for Perfluorooctanoic Acid (PFOA)**

Prepared by:

U.S. Environmental Protection Agency
Office of Water (4304T)
Health and Ecological Criteria Division
Washington, DC 20460

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ABBREVIATIONS AND ACRONYMS

ALT	alanine aminotransferase
ALP	alkaline phosphatase
APFO	ammonium perfluorooctanoate
AST	aspartate aminotransferase
AUC	area under the curve
BAF	bioaccumulation factor
BCF	bioconcentration factor
BMDL	benchmark dose level
BMF	biomagnification factor
bw	body weight
CAR	constitutive androstane receptor
CCK	cholecystokinin
CCL	Contaminant Candidate List
COPD	chronic obstructive airways disease
CWA	Clean Water Act
DWEL	drinking water equivalent level
DWI	drinking water intake
EPA	U.S. Environmental Protection Agency
FXR	farnesoid X receptor
GFR	glomerular filtration rate
GGT	gamma-glutamyl transferase
HA	Health Advisory
HDL	high-density lipoprotein
HED	human equivalent dose
HESD	Health Effects Support Document
IgM	immunoglobulin M
IRIS	Integrated Risk Information System
K _{oc}	organic carbon-water partitioning coefficient
K _{ow}	octanol-water partition coefficient
LCT	Leydig cell tumor
LC/MS/MS	liquid chromatography/tandem mass spectrometry
LDL	low-density lipoprotein
LOAEL	lowest observed adverse effect level
MOA	mode of action
MRL	minimum reporting level
ng/L	nanograms per liter
NHANES	National Health and Nutrition Examination Survey
NOAEL	no observed adverse effect level
PAC	powdered activated carbon
PACT	pancreatic acinar cell tumors
PBPK	physiologically based pharmacokinetic model
PFAS	perfluoroalkyl substance
PFC	perfluorinated compounds
PFOA	perfluorooctanoic acid
PFOS	perfluorooctanesulfonic acid

PTFE	polytetrafluoroethylene
pg/L	picograms per liter
PND	post-natal day
POD	point of departure
POE	point-of-entry
POU	point-of-use
PPAR α	peroxisome proliferator activated receptor alpha
PWS	public water system
PXR	pregnane X receptor
REACH	Registration, Evaluation, Authorization, and Restriction of Chemicals
RfD	reference dose
RSC	relative source contribution
SDWA	Safe Drinking Water Act
SNUR	Significant New Use Rule
SRBC	sheep red blood cell
TMF	trophic magnification factor
TNSSS	Total National Sewage Sludge Survey
UCMR 3	third Unregulated Contaminant Monitoring Rule
UF	uncertainty factor
UV	ultraviolet

EXECUTIVE SUMMARY

Perfluorooctanoic acid (PFOA) is a synthetic, fully fluorinated organic acid; it is used in a variety of consumer products and in the production of fluoropolymers, and it is generated as a degradation product of other perfluorinated compounds. Because of strong carbon-fluorine bonds, PFOA is stable to metabolic and environmental degradation. PFOA is one of a large group of perfluoroalkyl substances (PFASs) that are used to make products more resistant to stains, grease, and water. These compounds have been widely found in consumer and industrial products, as well as in food items. Major U.S. manufacturers voluntarily agreed to phase out production of PFOA by the end of 2015. Exposure to PFOA in the United States remains possible due to its legacy uses, existing and legacy uses on imported goods, degradation of precursors, and extremely high persistence in the environment and the human body. PFOA was detected in blood serum in 99% of the U.S. general population between 1999 and 2012; however, the levels of PFOA in blood have been decreasing since U.S. companies began to phase out production. Water resources contaminated by PFOA have been associated with releases from manufacturing sites, industrial sites, fire/crash training areas, and industrial or municipal waste sites where products are disposed of or applied.

The U.S. Environmental Protection Agency (EPA) is issuing a lifetime drinking water Health Advisory (HA) for PFOA of 0.07 micrograms per liter ($\mu\text{g/L}$) based on a reference dose (RfD) derived from a developmental toxicity study in mice; the critical effects included reduced ossification in proximal phalanges and accelerated puberty in male pups following exposure during gestation and lactation. PFOA is known to be transmitted to the fetus in cord blood and to the newborn in breast milk. This lifetime HA is based on the latest health effects information for noncancer and cancer effects for PFOA as described in EPA's 2016 *Health Effects Support Document for Perfluorooctanoic Acid (PFOA)*, which was revised following external peer review. Because the developing fetus and newborn are particularly sensitive to PFOA-induced toxicity, the RfD based on developmental effects also is protective of adverse effects in adults (e.g., liver and kidney toxicity). The lifetime HA is therefore protective of the population at large.

For PFOA, oral animal studies of short-term, subchronic, and chronic duration are available in multiple species including monkeys, rats and mice. These studies report developmental effects (survival, body weight changes, reduced ossification, delays in eye opening, altered puberty, and retarded mammary gland development), liver toxicity (hypertrophy, necrosis, and effects on the metabolism and deposition of dietary lipids), kidney toxicity (weight), immune effects, and cancer (liver, testicular, and pancreatic). Overall, the toxicity studies available for PFOA demonstrate that the developing fetus is particularly sensitive to PFOA-induced toxicity. Human epidemiology data report associations between PFOA exposure and high cholesterol, increased liver enzymes, decreased vaccination response, thyroid disorders, pregnancy-induced hypertension and preeclampsia, and cancer (testicular and kidney).

To derive candidate RfDs, EPA used a peer-reviewed pharmacokinetic model to calculate the average serum concentrations associated with candidate no observed adverse effect levels (NOAELs) and lowest observed adverse effect levels (LOAELs) from six studies for multiple effects. Consistent with EPA's guidance *A Review of the Reference Dose and Reference*

Concentration Processes (USEPA 2002), EPA applied protective uncertainty factors to address intraspecies variability, interspecies variability, and LOAEL to NOAEL extrapolation.

From a national perspective, the dominant source of human exposure to PFOA is expected to be from the diet; indoor dust from carpets and other sources also is an important source of exposure, especially for children. The HA was calculated using a relative source contribution (RSC) of 20%, which allows for other PFOA exposure sources (e.g., dust, diet, air) to make up 80% of the RfD.

EPA's risk assessment guidelines reflect that, as a general matter, a single exposure to a developmental toxin at a critical time in development can produce an adverse effect (USEPA 1991). In addition, short-term exposure to PFASs can result in a body burden that persists for years and can increase with additional exposures. Thus, EPA recommends that the lifetime HA for PFOA of 0.07 µg/L apply to both short-term (i.e., weeks to months) scenarios during pregnancy and lactation, as well as to lifetime-exposure scenarios.

Adverse effects observed following exposures to PFOA and PFOS are the same or similar and include effects in humans on serum lipids, birth weight, and serum antibodies. Some of the animal studies show common effects on the liver, neonate development, and responses to immunological challenges. Both compounds were also associated with tumors in long-term animal studies. The RfDs for both PFOA and PFOS are based on similar developmental effects and are numerically identical; when these two chemicals co-occur at the same time and location in a drinking water source, a conservative and health-protective approach that EPA recommends would be to compare the sum of the concentrations ([PFOA] + [PFOS]) to the HA (0.07 µg/L).

Under EPA's *Guidelines for Carcinogen Risk Assessment* (USEPA 2005), there is Suggestive Evidence of Carcinogenic Potential for PFOA. Epidemiology studies demonstrate an association of serum PFOA with kidney and testicular tumors among highly exposed members of the general population. Two chronic bioassays of PFOA support a positive finding for the ability of PFOA to be tumorigenic in one or more organs of rats, including the liver, testes, and pancreas. EPA estimated a cancer slope factor of 0.07 per milligram per kilogram-day (mg/kg-day)⁻¹ based on testicular tumors, and confirmed that the lifetime HA based on noncancer effects is protective of the cancer endpoint.